REMARKS

Claims 1-6 and 8-14 are pending to which the Examiner has provided the following rejections that the Applicants rebut in the following order:

I. Rejections Under 35 U.S.C. § 102(e)

A. Claims 1-6 and 8-14 are rejected as allegedly being anticipated by United States Patent No. 6,821,770 To Hogan et al.

B. Claims 1-6 and 8-14 are rejected as allegedly being anticipated by United States Patent No. 6,228,575 To Gingeras et al.

II. Rejections Under 35 U.S.C. § 103(a)

A. Claims 1-5 and 8-13 are rejected as allegedly unpatentable over Kuipers, *Current Opinion in Biotechnology* 10:511-516 (199) in view of Greisen et al., *J Clin Microbiol.* 32:335-351 (1994).

B. Claims 6 and 14 are rejected as allegedly unpatentable over Kuipers, *Current Opinion in Biotechnology* 10:511-516 (199) in view of Greisen et al., *J Clin Microbiol.* 32:335-351 (1994), and in further view of Arfin et al., *J Biol Chem* 275:29672-29684 (2000).

I. The Claims Are Not Anticipated

As the Examiner is well aware, a single reference must disclose each limitation of a claim in order for that reference to anticipate the claim. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). This criterion is not met with either the Hogan et al. or Gingeras et al. references.

A. Hogan et al. Does Not Anticipate Claims 1-6 and 8-14

The Examiner has pointed to various citations within Hogan et al. in an attempt to find the Applicants' ratio calculations. The Applicants disagree because Hogan et al. is simply determining the sensitivity at which a single signal is detectable above a background noise level. The Applicants' clearly contemplate a calculation of a ratio between two different signals generated from two different labels.

Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 1 and 9 by clarifying that the target DNA comprises a "first label" and the reference DNA comprises a "second label" and deleting step (c), simply to clarify this embodiment. Further, the Applicants' have further amended Claim 1 to identify that the arrayed genomic sequences are selected at "random" and are sized in the range of 1 – 2 kb. *Applicants' Specification pg 6 ln 14-21, and pg 32 ln 9.* New claims 22-25 identify the number of arrayed elements. *Applicants' Specification pg 7 ln 5, and pg 32 ln 20-21.* New claims 26 and 27 re-present ratio calculations of the first and second labels. These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Applicants submit that Hogan et al. does not contemplate using "random" nucleic acids and emphasizes that ribosomal nucleic acids must be employed:

> Each of the addresses includes at least one probe that hybridizes ribosomal nucleic acids from at least one microbial species under high stringency hybridization conditions.

Hogan et al., col 3 ln 21-23 [emphasis added]. Hogan et al. cannot be practiced using random nucleic acids because the method is dependent upon identifying microbes by identifying complementary ribosomal nucleic acid sequences:

> Herein is described a matrix-based microbe identification method that employs combinations of polynucleotide probes that hybridize the ribosomal nucleic acids from microorganisms. Probes in the matrix distinguish between organisms that differ from each other by known phylogenetic relationships.

Hogan et al., col 9, ln 50-55. The Applicants submit that Hogan et al. does not anticipate the Applicants' claimed embodiment and respectfully request that the Examiner withdraw the present rejection.

B. Gingeras et al. Does Not Anticipate Claims 1-6 and 8-14

The Examiner has improperly maintained the anticipation rejection to Gingeras et al. because the Examiner has not rebutted the Applicants' previous claim amendments and argument related to the calculation of a ratio using differentially labeled reference DNA and target DNA. In particular, the Examiner has not provided any evidence to maintain the rejection by pointing to any citations within Gingeras et al. in an attempt to find the Applicants' claimed element.

Moreover, similar to Hogan et al., Gingeras et al. cannot be practiced using random nucleic acid sequences:

> Initially, target nucleic acids derived from Mycobacterium species having rpoB genes of known sequence and known drug resistance are screened against a solid phase probe array derived from sequences complementary to the *Mycobacterium tuberculosis* rpoB gene (the *Mtb* rpoB chip). The known sequences are either available from the literature of can be independently established by another method, such as dideoxynucleotide sequencing.

Gingeras et al., col 9 ln 26-31 [emphasis added]. While the Examiner believes that Gingeras et al. may contemplate using almost any gene, it is clear that the sequence of the selected gene must be known. This is not the case for the randomly arrayed sequences recited in the Applicants' claimed embodiment.

The Applicants submit that Gingeras et al. does not anticipate the Applicants' claimed embodiment and respectfully request that the Examiner withdraw the present rejection.

II. The Claims Are Not Obvious

To establish a *prima facie* case of obviousness, three basic questions are evaluated. First, are there any suggestions or motivations, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference? Second, is there a reasonable expectation of success? Finally, does the prior art reference (or references when combined) must teach or suggest all the claim limitations? *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness.

A. Claims 1-5 & 8-13 Are Not Obvious Over Kuipers & Greisen et al.

1. The Examiner Overstates Kuipers

The Examiner overstates the teachings of Kuipers as follows.

> Kuipers et al. teaches producing a specific DNA array for the rapid identification of pathogens and spoilage bacteria ... (see page 512, 2nd column, 2nd paragraph).

Office Action pg 11. Kuipers et al. only provides a general review in the field of food biotechnology directed at various selection processes for bacteria that improve food preservation. The Examiner erroneously believes that Kuipers et al. teaches a method to identify bacterial species when merely speculating that:

> Of course, specific DNA arrays can be developed for various other purposes, for example, rapid identification of pathogens and spoilage bacteria ...

Kuipers, pg. 512, rhc. Such as statement does not render all DNA arrays obvious. In particular, Kuipers gives no guidance as to whether a bacterial species may be successfully identified using a random array of 1-2kb nucleotides. In fact, Kuipers advocates using nucleotides having a known sequence:

> Another straightforward way of producing DNA microarrays is to spot amplicons of each ORF annotated in the genome of interest ...

and,

> a fast increase in sequencing data is also taking place (Table 1), creating exciting possibilities ...

Kuipers, pg. 512 rhc. Each of these passages provides explicit teachings that microarrays should be provided with known nucleotide sequences. The Applicants disagree. The Examiner is directed towards "The Tiedje Declaration" explaining that the present invention is not only counterintuitive to conventional thinking, but has numerous practical advantages. Consequently, Kuipers does not provide teachings that make the

Applicants' claimed embodiment obvious. The Applicants respectfully request that the Examiner withdraw Kuipers as a cited reference.

Further, the Examiner has made a fundamental error in applying the teachings of Kuipers to the Applicants' claimed embodiment by stating that:

> Kuipers exemplifies that different cDNA strains can be differentially labeled and used in one combined sample for hybridization providing the possibility of multiplexing and allowing for several different cDNA samples (see page 512, 2nd column, 1st paragraph).

Office Action pg 11. When taking the entire paragraph into context, it is clear that Kuipers was not discussing bacterial identification methods, but simple microarrays designed to detect relative gene expression rates:

> DNA microarrays provide a powerful tool for analyzing transcription profiles of whole genomes ... Amplicons can conveniently be generated by PCR ... Fluorescently labeled cDNA is used or hybridization to the DNA arrays ... The wild-type and mutant-strain cDNAs can be differentially labeled and used in one combined sample for hybridization, providing the attractive possibility of multiplexing. This will even allow the simultaneous data acquisition of several different fluorescent dyes that can be used. <u>The data obtained provide information on differential gene expression.</u>

Kuipers, pg 512 1st column, 1st full paragraph through 2nd column 1st partial paragraph [emphasis added]. Kuipers has not introduced the concepts of a test bacterial DNA and a reference bacterial DNA for the purpose of identifying microbial species. Further, Kuipers has not introduced the concept that a random array of nucleic acids may be used to identify a microbial species.

Greisen also fails to contemplate any embodiments to identify a microbial species that utilizes <u>random</u> nucleic acids. The Applicants have compared their random array analysis with traditionally used identification protocols using ribosomal DNA sequences (such as that described in Greisen):

> Cluster analysis grouped the test strains in agreement with other types of experimental data (16S rDNA sequences) and % DNA-DNA homology).

Applicants' Specification, pg 7 ln 11-12. The Examiner should now realize that the presently claimed embodiment was compared to technologies described in the cited references in order to verify the new random array analysis.

Consequently, the asserted combination fails to teach all the elements and, concomitantly, cannot teach any reasonable expectation of success that an array comprising a random array of nucleic acids could, or should, be used to identify a microbial species.

Consequently, the Examiner has not found that the Kuipers-Greisen combination shows the Applicants' claimed embodiment as a predictable use of prior art elements according to their established functions. The Applicants respectfully request that the Examiner withdraw the present rejection.

B. Claims 6 and 14 Not Obvious Over Kuipers et al., Greisen et al., And Arfin et al.

The Examiner introduces Arfin et al. against two dependent claims 6, and 14 for teachings related to statistical analysis. The above argument and claim amendments make this rejection moot.

The Applicants respectfully request that Examiner to withdraw the present rejection.

.CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

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